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Sleep architecture in infants with spinal muscular atrophy type 1

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ABSTRACT

Objective: Few reports on sleep patterns of patients with spinal muscular atrophy type 1 (SMA1) have been published and none on sleep microstructure. The aim of this study was to analyze sleep architecture and microstructure in a group of infants with SMA1, compared with age- and sex-matched controls.
Methods: Twelve SMA1 patients (six males, mean age 5.9 months) and 10 controls (five males, mean age 4.8 months) underwent full polysomnography to evaluate their sleep architecture and microstructure by means of the cyclic alternating pattern (CAP).
Results: Compared with control children, SMA1 patients showed increased sleep latency and apnea/hypopnea index. CAP analysis revealed a significant increase in the percentage of A1 CAP subtypes, a reduction of that of A3 subtypes and of A2 and A3 indexes (number/h), indicating a dysfunction of the arousal system in these patients.
Conclusion: The results indicate the presence of an abnormality of sleep microstructure in SMA1 patients, characterized by a reduction of A2 and A3 CAP subtypes. We hypothesize that SMA1 patients have reduced arousability during non-rapid eye movement sleep, which could be interpreted as additional evidence of central nervous system involvement in this disease.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem [1]. It has an estimated incidence of 1 in 6000 to 1 in 10,000 live births and with a carrier frequency of 1 in 40 to 1 in 60 [2,3]. The gene responsible for SMA has been located within the complex genomic region at chromosome 5q11.2–q13.3, which contains a 500 kb inverted duplication [4,5].

The phenotype expression of the disease, inversely proportional to the amount of complete survival motor neuron 1 (SMN1) protein, ranges from severe generalized paralysis and need for ventilatory support from birth to relatively mild conditions presenting in young adults.

However, SMA type 1 (SMA1) is a very severe condition in which the affected infant never attains the ability to sit independently, is affected by severe chest infections with acute respiratory failure, and usually dies before the second birthday [6,7].

Sleep breathing disorders are an additional cause of morbidity and impaired quality of life in these children who have been reported to present with significantly more sleep apnea and thoracoabdominal asynchrony during the inspiratory and expiratory phases of both quiet and active sleep [8].

There are very few studies of sleep patterns in patients with SMA, and especially in subjects with SMA1 [9]. In a polysomnographic (PSG) study of 32 neuromuscular patients, four with a form of SMA sleep architecture revealed an increase in stage 1 sleep coupled with a decrease or absence of rapid eye movement (REM) sleep [10].

Another study on seven SMA children (six with SMA type 1.5–1.8, 1 with SMA type 2) showed impaired sleep architecture, but compensated nocturnal and diurnal gas exchange; in these cases, nocturnal non-invasive ventilation (NIV) resulted in a significant improvement of sleep architecture with higher sleep efficiency, decreased light sleep counterbalanced by increased deep sleep, longer REM sleep, and significantly fewer electroencephalographic (EEG) arousals [11].

All these previous studies only evaluated sleep stage architecture, and, to the best of our knowledge, no current studies have

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evaluated sleep microstructure by means of cyclic alternating pattern (CAP) analysis.

The aim of this study was to evaluate sleep architecture in a group of patients with SMA1, compared to an age- and sex-matched control group, and to analyze CAP parameters and the eventual effect of the respiratory events on CAP.

2. Methods

2.1. Subjects

We studied 12 infants with DNA-deletion-confirmed SMA1 referred to the Respiratory Unit of the Bambino Gesù Research Children's Hospital in Rome (six males; mean age ± SD, 5.9 ± 3.38 months; range, 2–12) and 10 age-matched controls (five males; mean age ± SD, 4.8 ± 3.29 months; range, 2–12). Controls were recruited from our database of subjects who had undergone a PSG study to exclude sleep-disordered breathing, respiratory and/or sleep disturbances.

Exclusion criteria for controls were: (1) neurological or genetic disorder or craniofacial anomaly, (2) abnormal growth or development, (3) history of seizures, (4) pre-existing lung disease, and (5) any sign of respiratory tract infection within the last 2 weeks.

The ethics committees of all the institutions involved in the study approved the protocol and the parents of all children gave their written informed consent.

2.2. Polysomnography

For both groups (patients and controls), PSG was carried out in a quiet room with video monitoring, after one adaptation night that did not include a full PSG in order to minimize the first-night effect. All recordings started at the patients' usual bedtime and continued until spontaneous awakening.

No hypnotic drugs were allowed for at least two weeks before sleep recording. All patients were accompanied by one of their parents throughout the night.

The EEG recordings and electrode placement were performed according the 10–20 system and the PSG montage included at least six EEG channels Fp1, Fp2, C3, C4, O1 and O2 (referred to the contralateral mastoid), left and right electro-oculogram (EOG), chin electromyogram (EMG), electrocardiogram (ECG), electromyogram of left and right tibialis anterior muscles, nasal cannula, thoracic and abdominal respiratory effort (inductance plethysmography), peripheral capillary oxygen saturation (SpO_2) and transcutaneous partial pressure of carbon dioxide ($tcPCO_2$) (TCM 4, Radiometer, Copenhagen, Denmark) measurements.

The recordings were carried out using a computerized workstation (E-series, Compumedics, Melbourne, Australia) scored manually and interpreted according to current guidelines [12,13].

The $tcPCO_2$ device was calibrated before every measurement and adjusted to the patients' PCO_2. No oxygen was supplemented or respiratory stimulants used.

Sleep was subdivided into 30 s epochs and sleep stages were scored according to the standard American Academy of Sleep Medicine (AASM) criteria [13]. Awakenings were polygraphically identified by two or more consecutive epochs scored as wakefulness, surrounded by epochs of sleep.

According to Terzano et al. [14], CAP was defined as a periodic EEG activity of non-REM (NREM) sleep characterized by repeated spontaneous sequences of transient events (phase A), recurring at intervals up to 2 min in duration. The return to background activity identifies the interval that separates the repetitive elements (phase B). In particular, A-phase candidates are scored within a CAP sequence only if they precede and/or are followed by another phase A in the temporal range of 2–60 s. If there were three consecutive A-phases followed by a non-CAP condition, the CAP sequence was stopped at the end of the second B-phase and the third A-phase A was quantified as non-CAP.

To adapt CAP scoring for the age of the subjects included in this study, the criteria reported by Miano et al. were adopted [15]. CAP cannot be scored in a recording if it is not possible to recognize K complexes, delta bursts, and/or spindles. Spindles are usually first present by 46–48 weeks conceptional age, whereas K complexes first appear 5 months post term and slow wave activity of slow wave sleep is first seen as early as 2–3 months post term and is usually present 4–4.5 months post term. Therefore CAP can be scored only when at least rudimentary spindles appear and slow wave activity emerges from high-voltage slow activity (HVS). For these reasons, in order to correctly score CAP in our subjects, following the classification of EEG patterns reported by Miano et al. we ensured that all subjects showed a sleep EEG pattern characterized by the appearance of sleep spindles mixed with delta and theta waves that could be scored as NREM sleep. No subjects with EEG pattern of 'tracé alternant' or high-voltage slow activity (HVS) were included.

The CAP subtype scoring criteria for infants were adopted as follows:

Subtype A1: A-phases in which slow EEG synchrony is the predominant activity, mostly comprising high-voltage delta bursts. Phasic activities initiating phase A must be one-third higher than the background voltage (calculated during the 2 s before the onset and 2 s after the offset of phase A).

Subtype A2: A-phases that contain a mixture of slow and fast EEG activities, including bursts of theta rhythms, associated or not with EMG activation; delta wave bursts followed by theta; and other faster rhythms. Subtype A2 may be linked with a moderate increase of muscle tone, cardiorespiratory rate, or both.

Subtype A3: A-phases in which the EEG activity is predominantly fast low-voltage rhythms with >50% of phase A occupied by fast EEG activities, including EEG arousals, polyphasic bursts, and high-voltage delta waves with an amplitude one-third higher, or more, than the background activity, followed by theta and other faster rhythms.

The following CAP parameters were derived: CAP rate (percentage of total NREM sleep time occupied by CAP sequences); number and duration of CAP cycles; number and duration of CAP sequences; number, duration and percentage of each A-phase subtype; A1, A2 and A3 index (number of phases A1, A2 or A3 per hour of NREM sleep); and number and duration of B-phases.

The apnea/hypopnea events were counted according to the criteria established by the AASM manual [13] and the ATS [12]: an obstructive apnea was defined as the absence of airflow, with continued chest wall and abdominal movement, for a duration of at least two breaths; mixed apnea was defined as apnea that usually begins as central and ends in obstruction according to changes in the chest, abdominal, and flow traces; hypopnea was defined as a decrease in nasal flow of ≥50% associated with a decrease in arterial blood oxygen saturation (SaO_2) of ≥3%, awakening or arousal; the apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time (TST). For this study, sleep-disordered breathing was defined as AHI ≥1.

All recordings were visually scored by one of the investigators (E.V.), and the sleep parameters derived were tabulated for statistical analysis.

2.3. Statistical analysis

Age and respiratory parameters of the subjects of the two groups were compared using Student's *t*-test, whereas sleep stage architecture and CAP parameters were compared by means of the

Table 1
Age and cardiorespiratory parameters of the subjects.

Variable	Controls ($n = 10$)		SMA1 ($n = 12$)		P-value[a]
	Mean	SD	Mean	SD	
Age (months)	4.8	3.29	5.9	3.38	NS
Mean SpO_2	97.7	1.41	97.2	1.74	NS
Minimum SpO_2	86.9	2.80	88.9	5.04	NS
T < 90%	0.12	0.13	1.64	5.82	NS
AHI	0.68	0.46	4.77	3.59	<0.003
Heart rate	109.8	13.72	110.2	19.49	NS
$tcPCO_2$	40.1	2.8	38.2	3.34	NS

SMA1, spinal muscular atrophy type 1; SD, standard deviation; SpO_2, peripheral blood oxygen saturation; T < 90%, percentage of total sleep time spent with SpO2 < 90%; AHI, apnea–hypopnea index; $tcPCO_2$, transcutaneous partial pressure of carbon dioxide.
[a] Student's t-test.

analysis of covariance using age as a covariate. Differences were considered statistically significant at $P < 0.05$. The commercially available software Statistica (version 6, StatSoft Inc., Tulsa, OK, USA) was used for all statistical tests.

3. Results

No differences were found in patient group composition, with respect to gender ($\chi^2 = 0$, not significant) and age (Table 1). No preterm infants were present in the patients group.

3.1. Cardiorespiratory pattern

Only AHI was significantly higher in the SMA1 group than in the control group. No significant differences were found between the two groups for the other cardiorespiratory parameters considered in this study.

3.2. Sleep stage architecture and sleep microstructure

Only the sleep onset latency was found to be significantly increased in SMA1 patients; the remaining sleep architecture parameters were not significantly different between SMA1 patients and control subjects (Table 2).

Regarding sleep microstructure parameters, the SMA1 group showed a significant increase in A1% and A2 mean duration (Table 3), together with a significant reduction in A3%, A3 index, and A2 index. The CAP sequence mean duration was significantly increased in SMA1, with respect to the control group.

Table 2
Sleep architecture parameters.

Variable	Controls ($n = 10$)		SMA1 ($n = 12$)		P-value[a]
	Mean	SD	Mean	SD	
Time in bed (min)	507.9	134.75	564.5	131.10	NS
Sleep period time (min)	482.8	117.60	497.9	104.17	NS
Total sleep time (min)	392.7	103.44	404.8	67.82	NS
Sleep latency (min)	15.6	17.97	45.5	43.01	0.046
REM latency (min)	81.2	85.26	84.2	91.13	NS
Stage shifts/h	10.7	3.02	9.8	2.10	NS
Awakenings/h	5.2	3.06	4.5	2.29	NS
Sleep efficiency (%)	78.1	12.30	72.9	8.41	NS
Wake time (%)	18.5	11.32	17.7	9.28	NS
N1 (%)	4.5	3.37	8.1	4.29	NS
N2 (%)	44.7	17.86	29.9	14.55	NS
N3 (%)	18.4	9.41	26.9	10.38	NS
REM (%)	13.9	5.64	17.3	7.39	NS

SMA1, spinal muscular atrophy type 1; SD, standard deviation; REM, rapid eye movement; N1–N3, non-REM sleep stages; NS, not significant.
[a] Analysis of covariance: age used as a covariate.

Table 3
Sleep cyclic alternating pattern (CAP) parameters.

Variable	Controls ($n = 10$)		SMA1 ($n = 12$)		P-value[a]
	Mean	SD	Mean	SD	
Total CAP rate (%)	12.6	4.95	16.1	6.56	NS
N1 (%)	7.9	10.13	4.4	5.17	NS
N2 (%)	9.0	5.32	12.2	8.22	NS
N3 (%)	20.2	10.79	25.6	10.24	NS
A1 (%)	68.7	11.15	92.3	5.25	0.000015
A2 (%)	7.0	5.55	3.7	2.68	0.07
A3 (%)	24.3	10.54	4.0	3.51	0.000047
A1 mean duration (s)	8.0	2.45	11.7	2.78	NS
A2 mean duration (s)	10.7	2.21	13.7	3.38	0.011
A3 mean duration (s)	12.3	4.65	15.3	7.44	NS
A1 index	12.4	4.57	17.1	7.03	0.07
A2 index	1.1	0.61	0.4	0.53	0.05
A3 index	3.4	3.18	0.4	0.40	0.02
B-phase mean duration (s)	26.9	3.68	28.5	2.22	NS
CAP cycle duration (s)	35.5	5.09	40.4	3.14	NS
Sequence duration (s)	127.2	20.63	174.2	37.41	0.014
CAP sequences (no.)	19.1	7.81	18.3	6.92	NS

SMA1, spinal muscular atrophy type 1; SD, standard deviation; N1–N3, non-rapid eye movement sleep stages; A1–A3, CAP subtypes (see text); B phase, phase B of CAP duration; NS, not significant.
[a] Analysis of covariance: age used as a covariate.

4. Discussion

To our knowledge, this is the first study attempting to evaluate the sleep pattern in infants with SMA1 and to analyze their sleep microstructure by means of CAP. Our findings indicate the presence of a subtle but significant disruption of sleep architecture detected only by CAP microstructural parameters. Sleep stage architecture parameters in the SMA1 group showed no significant differences with respect to controls; only the sleep onset latency was slightly increased, probably due to the reduced spontaneous mobility of patients who remained in bed for a longer time than controls.

The limited literature on this topic seems to report several sleep architecture changes. Pradella showed an increase in stage 1 sleep, coupled with a decreased or absent REM sleep; however, these data cannot be fully compared to our findings because their study was conducted on 32 patients affected by different neuromuscular diseases, with only four of them presenting with a form of SMA. Another recent study on seven SMA children [11], prevalently affected by SMA type 2 and older (6–12 years) than our subjects, showed impaired sleep architecture, represented by an increase of light sleep (NREM stage 1 and 2), and by a decrease of slow-wave sleep (NREM stages 3 and 4) and REM sleep. In this series, nocturnal non-invasive ventilation resulted in a significant improvement of sleep architecture [11].

As expected, our SMA1 patients showed an AHI significantly higher than that of the control group, in agreement with previous studies that constantly found an AHI >1 in all SMA patients [8].

The severity of sleep-disordered breathing (SDB) is related to the residual lung function: it ranges from transient hypopneas during REM sleep to hypoventilation in advanced stages of the disease. SDB often precedes manifest diurnal respiratory failure by years, and causes sleep disturbance, restless sleep, nocturnal hypoxemia and CO_2 retention, inducing autonomic nervous system dysfunction and neurobehavioral daytime symptoms [8].

With our findings, we can hypothesize the presence of an involvement on the central nervous system in SMA1 that affects sleep microstructure parameters. CAP analysis showed an increase in slow EEG oscillations (A1% and A1 index) and a reduction of the A2 and A3 indexes (characterized by fast EEG activities). This finding seems to indicate that SMA1 patients have a decreased arousability; in fact,

CAP subtypes A2 and A3, which were found to be greatly reduced, correspond closely to arousals [16] as scored following the AASM criteria.

Some similarities may be noticed between the results of the present study and sleep features of infants with an apparent life-threatening event (ALTE) and obstructive sleep apnea.

ALTE was defined as "an episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging" [17].

Our infants show reduced heart rate response, altered heart rate and blood pressure variability and an increased arousal threshold in REM; by contrast, ALTE infants with normal sleep breathing have normal cardiovascular and arousal responses [18]. Several previous studies have supplied evidence that infants with ALTE have defective arousal responses to hypoxia [19–21], fewer arousals from sleep, and fewer body movements [22–25], although the reason for this is unknown. From this perspective, our data are in agreement with those reported by Franco et al. showing that, during NREM sleep, ALTE infants had fewer total arousals, cortical arousals, and subcortical activations at 2–3 and 5–6 months when compared to control infants.

Interestingly, we did not find correlations between AHI and CAP parameters. In children, respiratory events usually cause sleep disruption with an increase in arousals reflected by an enhancement of A2 and A3 CAP subtypes [26–28]. On the contrary, our patients had reduced A2 and A3 indices, indicating a decrease in their arousability. This finding might be interpreted as a central nervous system failure to arouse, and might also lead to the hypothesis of an involvement of the central nervous system in SMA1 patients, as already suggested by previous research [29–31].

Neuropathologically, the most important change in SMA1 is degeneration of spinal and brainstem motor neurons; the spinal ganglion, posterior root, Clarke's column, posterior funiculus and lateral thalamus are also affected, as well as the anterolateral portions of the thalamus [29]. Thus, SMA1 has been regarded as a multisystemic disease also involving the sensory system, despite the absence of clinical sensory disturbances. There is evidence that cells and tissues outside of the nervous system are also affected in SMA. The pathological findings in cells other than motor neurons, which are predominantly seen in more severe cases, have led to the development of the threshold hypothesis. This hypothesis proposes that there is a differential susceptibility of cells to survival motor neuron (SMN) depletion and that different cell types and tissues fall in different positions within a vulnerability-resistance spectrum [32].

The majority of SMA cases are caused by homozygous deletion of the *SMN1* gene, leading to reduced expression levels of full-length SMN protein [33]. It was demonstrated that significant levels of SMN protein have previously been identified in the brain [34,35], raising the possibility that reduced levels of expression may have effects on non-motor regions of the nervous system; a recent study showed reduced levels of SMN protein in regionally selective, impaired brain development in a mouse model of severe SMA. Data derived from animal studies show that high levels of SMN protein are required for normal brain development in vivo. Thus, reduced expression of SMN protein – down to levels sufficient to cause a severe form of SMA in mice – cause abnormal brain development, affecting regions such as the hippocampus [36].

Similarly, we can hypothesize that in human SMA1 the reduction of SMN protein in the brain impairs brain development, affecting regions of the central nervous system involved in arousal control. An involvement of the central nervous system has been suggested in a previous work on evoked potentials in children with SMA1 and SMA2. Somatosensory evoked potentials and brainstem-evoked response abnormalities were much more frequent in SMA1 than in SMA2 and may be related to a degenerative process affecting retrochiasmatic visual pathways [37]. These abnormalities of evoked potentials provide neurophysiologic evidence of central sensory system involvement in SMA, in agreement with the delayed thalamocortical conduction, indicating that afferent central nervous system pathways are involved in SMA1. We cannot exclude, therefore, that a reduction in sensory and proprioceptive inputs from external stimuli may lead to a decreased arousal response in our subjects.

One limitation of this study is the small sample size; however, it must be acknowledged that given the frequency and prevalence of SMA1, our group can be viewed as relatively large, although the generalizability of our results should be considered with some caution. We used an appropriate statistical approach in order to avoid a statistical type 1 error, but a type 2 error cannot be excluded. Another possible limitation was the expected variability of sleep patterns due to age, in the range 2–12 months, but we set up two groups well balanced in this regard.

In conclusion, our findings of reduced EEG arousability during sleep in infants with SMA1 might be further evidence of central nervous system involvement in this disease and might represent an additional risk factor for the premature death of these patients that is frequently attributed to the rapid progress of weakening of muscles and respiratory failure [38].

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.05.029.

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